

**Priority 1: Expand Therapeutic Options for Opioid Addiction, Overdose Prevention, and Reversal**

- 1) New formulations of existing medications to improve treatment compliance, prevent relapse, and reduce risk of misuse
  - NIH will support development of develop new treatment strategies for OUD, including longer-acting formulations of existing addiction treatment medications to promote adherence to treatment while preventing medication misuse.
- 2) Stronger, longer-duration formulations to counteract opioid overdose
  - NIH will support development of stronger, longer-acting formulations of opioid antagonists to reverse overdose.
- 3) Interventions against respiratory depression
  - NIH will support development of new classes of compounds and devices to counter respiratory depression induced by opioids alone or in combination with other substances.
- 4) Novel medications, immunotherapies, and devices to treat withdrawal, craving, progression, and relapse
  - NIH will support (Drug repurposing) new therapeutic approaches resulting from repurposing medications already approved for other indications for use in reducing opioid seeking, and evaluating medications already in use internationally but not in the United States.
  - NIH will support (Novel immunotherapies) coordinated studies to develop anti-opioid vaccines that induce high-affinity antibodies that bind target opioids.
  - NIH will support (Drug craving research) focused medication development efforts for treatment of OUD.
- 5) New medications targets for treatment of OUD
  - NIH will support preclinical target identification and validation efforts to help reveal new mechanisms of action for OUD treatment.

**Priority 2: Enhance Treatments for Infants with NAS/NOWS**

- 1) Advancing clinical trials in neonatal opioid withdrawal syndrome (ACT NOW)
  - NIH will support clinical trials to determine best clinical practices, including assessment of both drug-free treatment approaches and currently used medications.
- 2) Cognitive development of infants exposed to opioids
  - NIH will establish a large cohort of pregnant women from regions of the country significantly affected by the opioid crisis and follow them and their children for at least 10 years.

**Priority 3: Develop New or Improved Prevention and Treatment Strategies for Addiction**

- 1) Preventing at-risk adolescents from developing OUD as they transition into adulthood
  - NIH will support developing and testing strategies to prevent opioid misuse and addiction in at-risk older adolescents and young adults.
- 2) Understanding sleep dysfunction in OUD and recovery
  - NIH will support genomic, molecular, pharmacological, and clinical approaches that are appropriate to elucidate sleep and circadian factors relevant to addiction and to determine how these factors influence one another.
- 3) Management of subsyndromal and low-severity OUD
  - NIH will support studies of subsyndromal OUD and/or low-severity OUD in general medical settings.
- 4) Determining the optimal length of medication treatment for opioid addiction
  - NIH will conduct a randomized controlled clinical trial of two FDA-approved medications to treat opioid addiction: methadone and buprenorphine to help define the optimal duration of medication-based treatment for OUD, taking into account various patient populations and treatment settings.
- 5) Optimizing collaborative care for patients with OUD and common mental disorders
  - NIH will support testing the adaptation, effectiveness, adoption, scalability, and sustainability of collaborative care for individuals with OUD and co-occurring mental health conditions using integrated treatment models in primary care settings.

**Priority 4: Optimize Effective Treatment Strategies for Opioid Addiction**

- 1) Enhanced National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) for opioid research
  - NIH will support expansion of the network to develop, validate, refine, and translate into practice new treatment options for patients with substance use disorders. New research sites and investigators.
- 2) Opioid innovation in the criminal justice system
  - NIH will support studies on quality care for opioid misuse and OUD in justice populations by facilitating partnerships between local and state justice systems and community-based treatment providers.
- 3) Behavioral research to improve medication-based treatment for OUD
  - NIH will support studies on whether select behavioral interventions — such as mindfulness meditation, cognitive behavioral therapy, or multidisciplinary rehabilitation — improve adherence to medication-based treatment, improve medication-based treatment outcomes, and reduce relapse rates in individuals seeking treatment for OUD.

4) The HEALing Communities Study

- NIH will support testing the integration of prevention, overdose treatment, and medication-based treatment in select communities hard hit by the opioid crisis in a coordinated array of settings: primary care; emergency departments; specialty care, including prenatal care, infectious disease, and behavioral health; the criminal justice system; and other community settings.

**Priority 5: Understanding the Biological Underpinnings of Chronic Pain**

1) The Acute to Chronic Pain Signatures Program

- NIH will support studies to understand the biopsychosocial characteristics of people who are susceptible to making the transition from acute to chronic pain.

**Priority 6: Accelerate the Discovery and Preclinical Development of Non-Addictive Treatments for Pain**

1) Discover and validate novel targets for safe and effective pain treatment

- NIH will support multisite validation studies and multidisciplinary tools to reveal novel targets for the treatment of pain, encompassing all levels of the pain-processing pathway from a basic biology perspective.

2) Engineering preclinical testing platforms to identify and profile non-addictive therapeutics for pain and addiction

- NIH will support development of animal models that more closely reflect a variety of human pain conditions to test potential non-addictive treatments for acute and chronic pain management.
- NIH will support human cell-based screening platforms to accelerate development of novel drugs to treat pain, addiction, and overdose.

3) Translating discoveries into effective devices for pain treatment

- NIH will support target identification, late-stage translational therapeutic and diagnostic device development, verification and validation activities, and early clinical studies.

**Priority 7: Advance New Non-addictive Treatments for Pain through the Clinical Trial Pipeline**

1) Discovery and validation of biomarkers and endpoints for pain

- NIH will support biomarker discovery and rigorous validation to accelerate high-quality therapeutic development and move clinical research toward Phase 2 trials and beyond.

2) Testing of novel assets in an early-phase pain clinical trial network

- NIH will support projects that collect and evaluate pharmacological assets contributed by academia and by biopharmaceutical and medical device companies for their potential use as non-addictive treatments for pain and addiction.

## NIH HEAL Initiative Research Plan Priorities

### 3) NIH Back Pain Consortium

- NIH will support studies to better understand the mechanisms of common pain conditions, such as chronic low back pain; improve patient phenotyping; develop improved diagnostic and treatment tools; and identify, prioritize, and test mechanistically based therapies.

## **Priority 8: Establish the Best Pain Management Strategies for Acute and Chronic Pain Conditions**

### 1) Pain Management Effectiveness Research Network (ERN) for Clinical Trials

- NIH will provide infrastructure to conduct Phase 3 clinical trials designed to evaluate the effectiveness of pharmacologic and nonpharmacologic therapies for a broad array of acute and chronic pain conditions.

### 2) Integrated approach to pain and opioid use in patients undergoing hemodialysis

- NIH will support studies to develop and test multimodal, non-opioid treatment approaches that are tailored to the individual patient.

### 3) Pragmatic & implementation studies for the management of pain to reduce opioid prescribing

- NIH will support clinical research to integrate evidence-based interventions for pain into health care systems.